REMARKS

Telephone Interview with the Examiner

The Examiner is thanked for the courtesy she extended to coinventor, Dr. Nancy Camacho, Dr. Jahanara Ali (Director of Technology Transfer of the Hospital of Special Surgery) and the undersigned during a telephone interview held on September 22, 2004.

Prior to the telephone interview, a PowerPoint presentation was e-mailed to the Examiner by the undersigned. Dr. Camacho discussed said PowerPoint presentation with the Examiner during the telephone interview. Submitted concomitantly herewith is a DECLARATION UNDER 37 CFR 1.132 OF DR. NANCY P. CAMACHO. Attached to said DECLARATION is a copy of said PowerPoint presentation.

Form PTO/SB/08B dated August 22, 2001

In view of the REQUEST FOR FULLY INITIALED COPY OF FORM PTO/SB/08B filed on July 28, 2004, the Examiner is respectfully requested to return to the undersigned a fully initialed copy of sheet 3 of the Form PTO/SB/08B dated August 22, 2001.

Objection to the Disclosure

The disclosure was objected to in the second paragraph on page 2 of the Office Action because of the following alleged informality: "It is unclear as to where applicant provides a detailed description of Fig. 7A."

Fig. 7A is described on page 10, lines 9 to 16 and on page 23, lines 18 to 20 of the specification.

In view of the above, withdrawal of the objection to the disclosure is respectfully requested.

Presently Claimed Invention

The presently claimed invention concerns a method for the evaluation of the ultrastructure of connective tissue comprising:

(a) providing a fiber optic probe operative in the mid-infrared or near-infrared region of the electromagnetic spectrum,

(b) positioning the probe to be in contact with the surface of the connective tissue for detecting attenuated total reflectance or within a sufficient distance from the surface of the connective tissue for detecting reflection,

(c) detecting mid-infrared radiation or near-infrared radiation penetrating the surface of the connective tissue for

detecting attenuated total reflectance or reflecting off of the surface of the connective tissue for detecting reflection, and

(d) analyzing the infrared radiation from step (c) for at least one of peak height, peak area and frequency and comparing at least one of the peak height, the peak area and the frequency to established values for at least one of peak height, peak area and frequency for normal connective tissues to detect a modification in the molecular structure of the connective tissue, and determining the progression of degradation or repair of the connective tissue, the connective tissue being selected from the group consisting of cartilage, ligament, tendon, capsule and bone (see applicants' claim 1).

Obviousness Rejection

Claims 1 to 20 were rejected under 35 USC 103 as being obvious over Gadaleta et al., "Fourier Transform Infrared Microscopy of Calcified Turkey Leg Tendon", Calcif. Tissue Int., 58, 17-23, (1996) in view of Zakim USP 5,733,739 and Guzelsu et al. USP 6,324,419 for the reasons set forth in the paragraph bridging pages 2 and 3 of the Office Action.

Discussion of the References

Gadaleta et al.

One of the authors of the Gadaleta et al. reference is a co-inventor of the present invention, namely Dr. Nancy P. Camacho.

The following was stated at the top of page 3 of the July 8, 2004 Office Action:

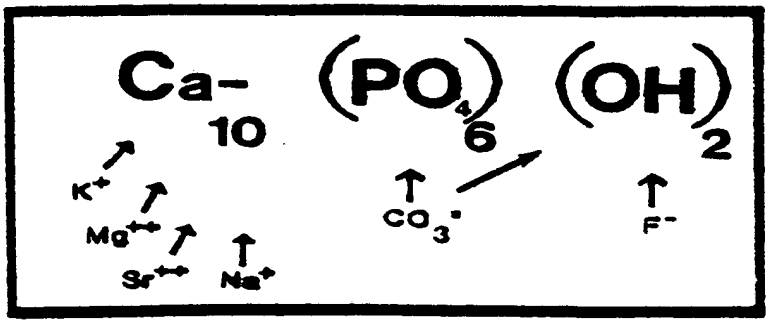
> "Gadaleta et al. discloses Fourier Transform Infrared Microscopy of Turkey Tendons. Analysis of the infrared spectrum can detect a modification in the molecular structure of the tendon and therefore determine the progression of degradation."

It is respectfully submitted that the interpretation of what is disclosed in Gadaleta et al. in the Office Action is incorrect for the following reasons.

Although the word "tendon" is in the title of the Gadaleta et al. reference, the study reported in Gadaleta et al., as clearly stated in the first sentence of the abstract of Gadaleta et al., was directed towards Fourier transform infrared ("FTIR") analysis of the "mineral phase" in calcified tendons. As described in Gadaleta et al. (paragraph 3 of the introduction on page 17), calcified turkey leg tendons are used as models of biological mineralization, and the study reported in Gadaleta et

al. utilized FTIR microscopy to analyze the spatial variations in the mineral phase, not in the tendon per se.

Biological mineral phases are typically composed of either calcium phosphate or calcium carbonate. In calcified tendon, the phase is similar to the calcium phosphate "hydroxyapatite" whose molecular formula appears as follows:



In that model of biological mineralization, the tendon is essentially a scaffold for the mineral, and the mineral can be analyzed by FTIR independently of the tendon structure. The Gadaleta et al. study evaluated spatial variations in the quantity and chemical structure of mineral present.

Infrared analysis has been widely utilized to study normal and pathological biological mineralization for over 40 years in many different model systems, including in sea shells (*1. J. Biomed. Mater. Res., 1999;48(5):749-754. "Fourier Transform*

Infrared Spectroscopy (FTIR) and X-ray Diffraction Analyses of Mineral and Organic Matrix During Heating of Mother of Pearl (nacre) from the Shell of the Mollusc Pinctada Maxima", Balmain, J., Hannoyer, B., Lopez, E.; 2. Spectrochim. Acta A Mol. Biomol. Spectrosc., *2000 June; 56A(7):1345-53, "EPR and IR Spectral Studies of the Sea Water Mussel Mytilus Conradinus Shells", Narasimhulu, K.V.; Rao, J.L.);* in teeth *(1.* Calcif. Tissue Int., *1999, Dec; 65(6):459-465, "A Comparative Infrared Spectroscopic Study of Hydroxide and Carbonate Absorption Bands in Spectra of Shark Enameloid, Shark Dentin, and a Geological Apatite"; 2.* Am. J. Dent., *2001 April; 14(2):63-66, "Effect of Carbamide Peroxide Bleaching Agents on the Physical Properties and Chemical Composition of Enamel", Cimilli, H., Pameijer, C.H.;* and in aortic calcifications (1. Pathologica., 1989, March-April; 81, (1072):139-149, "Artery Wall Calcification: Correlation of Atherosclerosis with Mineralization", Cichocki, T., Heck, D., Jarczyk, L., Rokita, E., Strzalkowski, A., Sych, M.; 2. Biochim. Biophys. Acta., 2003, July, 30; 1638(3):235-240, "In Vitro Effect of Cholesterol on Calcifying Activity of Vesicles Isolated from

Rabbit Aortas", Hsu, H.H.). Copies of these publications are enclosed herewith.

The above examples illustrate that FTIR spectroscopy of biological materials is an extremely broad field that encompasses many different areas of research, even just within the field of mineralization. The one commonality among all the aforementioned FTIR studies is that they involve evaluation of the vibrational spectrum obtained from a material. However, the specific focus of the studies can be extremely different.

In Gadaleta et al., FTIR was used to evaluate the mineral phase by examination of the spectrum that arises from the phosphate moiety in the mineral. In the presently claimed invention, FTIR is used to evaluate the degradation of cartilage and other connective tissues, and this is not related to whether or not a mineral phase is present. It is respectfully submitted that there is no path that would "obviously" relate the FTIR study of biological mineralization, a phenomenological study, to the clinical application of FTIR to evaluate connective tissue degradation.

Zakim et al.

It was admitted in the previous Office Action of April 6, 2004 that Zakim et al. fail to specifically disclose the use of a fiber optic probe and evaluation of connective tissue.

Zakim et al. do not specify any specific tissue. Furthermore, Zakim et al. do not disclose connective tissue as recited in applicants' claims, such as cartilage, ligament, tendon, capsule and bone. All the claims in Zakim et al. are directed to cells, not tissues.

The gist of Zakim et al. is to detect cancerous cells. Zakim et al. thus discuss PAP smear tests and dysplasia.

Zakim et al. evaluate only cells for pre-cancerous and cancerous changes or tissues affected by cancer or other diseases prior to obtaining a biopsy. Such alterations cannot be identified in connective tissue.

Zakim et al. do not concern tissue and specifically do not relate to any connective tissue, and more specifically is not directed to cartilage, ligament, tendon, capsule or bone.

In contrast to Zakim et al., in the presently claimed invention, changes in cells are not being evaluated but, rather,

the presently claimed invention is directed to determining the progression or repair of connective tissue selected from the group consisting of cartilage, ligament, tendon, capsule and bone. This has nothing to do with malignancy.

Guzelsu et al.

Guzelsu et al. do not disclose utilizing infrared radiation to evaluate molecular changes. In Guzelsu et al., a light source is utilized, but it is used such that it interacts with tissue, is reflected back, and the "amount" of light reflected back correlates with a bulk tissue property. There is no information in Guzelsu et al. concerning the molecular composition of the tissue being examined.

Guzelsu et al. concern the utilization of light scattering to evaluate skin. There is no teaching or suggestion in Guzelsu et al. regarding the specific connective tissues (cartilage, tendon, ligament, capsule or bone) recited in applicants' claims.

It is respectfully submitted that it is not obvious to go from evaluation of a bulk tissue property (as in Guzelsu et al.) to evaluation of a molecular tissue property as in the presently claimed invention, since molecular tissue properties are

numerous, at the molecular ultrastructural level, and quite complicated.

The differences between evaluating a bulk tissue property (assessed by light scattering) and a molecular property (assessed by spectroscopy), as in the presently claimed invention, are illlustrated in the last PowerPoint slide attached to the enclosed DECLARATION UNDER 37 CFR 1.132 OF DR. NANCY P. CAMACHO.

Applicants' Replies to Positions Taken in the Office Action

The following was alleged at the middle of page 3 of the July 8, 2004 Office Action:

> "It would have been obvious to one skilled in the art to have modified Gadaleta et al. such that the IR spectra analysis employs either infrared reflectance spectroscopy or infrared attenuated total reflectance techniques for evaluating tissue and performs the test either in vivo or in vitro."

Applicants respectfully disagree with the above contention, since the Gadaleta et al. studies are purely phenomenological studies on mineralization. Thus, one having ordinary skill in the art would not benefit by, or even think of, using those other techniques.

The following was stated on page 3, lines 4 to 5 of the July 8, 2004 Office Action:

> "Zakim et al. disclose using either infrared reflectance spectroscopy of infrared attenuated total reflectance techniques for evaluating tissue."

As discussed hereinabove, Zakim et al. disclose evaluating **cells**, not **tissue**. These are two very different materials, and hence are studied very differently. Also, as discussed hereinabove, the focus of Zakim et al. is the use of infrared to discriminate between cancerous and non-cancerous cells, i.e., the scientific analysis actually involves investigation of cellular changes, not tissues. Cancer diagnosis using the method of Zakim et al. involves the identification of differences in the cells present in the tissues, with the ultimate goal of being able to decide how much of the diseased tissue to excise.

In sharp contrast to Zakim et al., it is an object of the present invention to provide *in vitro* monitoring of the repair of connective tissue, such as cartilage, and to provide *in vitro* monitoring of the progression of degradation of connective tissue, such as cartilage. Monitoring the repair of a tissue

such as cartilage involves quantitation of ultrastrucutral tissue changes, such as obtaining information on molecular composition and orientation. Thus, applicants' claimed method is used to obtain three-dimensional information on the cartilage ultrastructure, which can be utilized to assess how well repair tissue or engineered matrices have integrated into the native cartilage. Therefore, the presently claimed invention is ultimately a method to assess the capability of cartilage, ligament, tendon, capsule or bone to regenerate or repair itself. This data will provide information on the mechanism of early chondral degeneration and repair.

The following position was set forth on page 3, lines 17 to 22 of the July 8, 2004 Office Action:

> Guzelsu et al. disclose using a fiber optic probe to optically examine connective tissue. It would have been obvious to one skilled in the art to have further modified Gadaleta et al. such that an optic fiber probe is used to examine the connective tissue/tendon as taught by Guzelsu et al. Such a modification m erely involves the substitution of one known type of probe having a light source for another."

As discussed hereinabove, Guzelsu et al. utilize a light source that interacts with tissue, is reflected back, and the "**amount**" of light reflected back correlates with a bulk tissue property. Guzelsu et al. does not provide any information concerning **the molecular composition** of the tissue examined.

With spectroscopy, in the technique employed in the presently claimed invention, individual frequencies are examined and are related to molecular strucure which is substantially different from just looking at the quantity of light (radiation). It is specifically recited in applicants' claim 1 "to detect a modification in the molecular structure of the connective tissue."

*I*n Guzelsu et al., the amount of light correlates with the amount of "stretch" in a connective tissue, skin. This may provide information on some "macroscopic" structures of a sample, but certainly no information on individual molecules.

Applicants' claimed invention utilizes infrared spectroscopy to analyze molecules in tissue, not to analyze bulk tissue. An

infrared spectrum gives information on the molecules in the tissue, not on bulk tissue property, or even on the macroscopic structure of the tissue. The peak shifts (frequency changes) recited in applicants' claims are related to molecular vibrations. It is a well-known and extremely well-documented fact in the scientific literature that spectroscopy is a separate field from light scattering or the quantitation of reflective light. Thus, it is respectfully submitted that it is not an obvious step to substitute an infrared probe for an optical light probe.

It is therefore respectfully submitted that applicants' claimed invention is not rendered obvious over the references, either singly or combined in the manner relied on in the Office Action, in view of the many distinctions discussed hereinabove. It is furthermore submitted that there are no teachings in the references to combine them in the manner relied upon in the Office Action.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Enclosures: (1) DECLARATION UNDER 37 CFR 1.132 OF DR. NANCY P. CAMACHO dated October 5, 2004

(2) Copies of J. Biomed. Mater. Res., (1999), 48(5):749-754; Spectrochim. Acta. A. Mol. Biomol. Spectrosc., June 2000, 56A(7):1345-1353; Calcif. Tissue Int., Dec. 1999, 65(6):459-465; Am. J. Dent., Apr. 2001, 14(2):63-66; Pathologica, Mar-Apr. 1989, (1072):139-149; and Biochim. Biophys. Acta., July 30, 2003, 1638(3):235-240